

inhalation studies comparing insulin administration by aerosol inhalation (using cumbersome devices) and by subcutaneous injection for the reproducibility of dosing have shown that the variability in glucose response to the two methods was equivalent. Bioavailability in more recent studies with aerosol insulin was up to 25%, supporting the use of such a method of administration. Laube, B. L.; Georgopolos, A.; Adams, G. K. *J. Am. Med. Assoc.* **1993**, 269, 2106. Insulin administered by oral inhalation effectively normalized diabetic patients' plasma glucose levels without adverse effects. Numerous patents have issued, directed to methods, formulations and devices for the oral administration of insulin via inhalation therapy. See, for example, U.S. Patents Nos. 5,952,008; 5,858,968; and 5,915,378, the disclosures of which are hereby incorporated specifically by reference.

Please replace paragraph [000111] with the following paragraph:

[000111] Fifteen minutes of global ischemia followed by twenty minutes of reperfusion resulted in prolonged ventricular dysfunction characterized by reduced levels of LVP generation as well as significant decreases in dP/dt_{max} and dP/dt_{min} . Pretreatment with rFGF-2 significantly improved the extent of recovery of LVP compared with control (untreated) hearts (83 ± 5 vs. $61 \pm 6\%$) and equally significant preservation of dP/dt_{max} and dP/dt_{min} (86 ± 3 vs. $65 \pm 6\%$ and 85 ± 5 vs. $60 \pm 5\%$, respectively). Stunning in hearts perfused with either NOS inhibitor by itself was not different from that in control hearts. Functional recovery of LVP in untreated control hearts ($61 \pm 6\%$) was not significantly different from that in hearts perfused with either L-NAME alone ($59 \pm 9\%$) or L-NIL alone ($57 \pm 6\%$). Depression of dP/dt_{max} and dP/dt_{min} (65 ± 6 and $60 \pm 5\%$, respectively) in untreated hearts was similar to that in hearts perfused with L-NAME alone (60 ± 9 and $55 \pm 8\%$, respectively) and hearts perfused with L-NIL alone (57 ± 9 and $67 \pm 4\%$, respectively).

Please replace the paragraph before paragraph [000115] with the following paragraph:

[000114] *Ischemia and reperfusion.* The hearts were subjected to no-flow ischemia for 15 min. The organ bath was evacuated of its oxygenated solution and refilled with nitrogen-saturated perfusate. Pacing was maintained during ischemia. LV pressure was monitored throughout ischemia and reperfusion. All hearts ceased to contract within 3 min. The time for LVP to fall to 10% of baseline (T_{LVP10}) was measured to quantify differences in LV function during early ischemia. Mean ischemic Ca_i^{2+} was calculated as the mean Ca_i^{2+} recorded from the 2nd through the 14th minute of ischemia. Contracture was defined as an abrupt and sustained rise in intraventricular pressure above 4 mmHg. Contracture time was measured as the time from the onset of ischemia to the onset of contracture. At the end of 15 min of ischemia, the nitrogen-saturated bath was replaced by the original bath maintained at 30°C. Flow was recommenced. Mean Ca_i^{2+} during early reflow was calculated as the mean of the peaks of Ca_i^{2+} recorded during the 1st minute of reperfusion. After 20 min of reperfusion, Ca_i^{2+} and functional parameters were again measured.

Please replace paragraph number [000119] with the following paragraph:

[000119] *Quantification of NOS Gene Expression* To determine NOS2 and NOS3 mRNA levels in FGF-2-treated compared with control hearts, 30 cycles of RT-PCR were performed on equal amounts of total RNA from six control and six rFGF-2-treated hearts using primers corresponding to human NOS3 and NOS2 sequences. For NOS3, primers were as follows: 5' (sense), 5'-CAGTGTCCAACATGCTGCTGGAAATTG-3' (bases 1,050-1,076) (SEQ ID NO: 1); antisense, 5'-TAAAGGTCTTCTTGGTGATGCC-3' (bases 1,511-1,535) (SEQ ID NO: 2). For NOS2, primers were as follows: 5' (sense), 5'-GCCTCGCTCTGGAAAGA-3' (bases 1,425-1,441) (SEQ ID NO: 3); antisense, 5'-TCCATGCAGACAACCTT-3' (bases 1,908-1,924) (SEQ ID NO: 4). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA was amplified

from the same amount of RNA at the same time to correct for variation between different samples. The PCR products, separated on 1% agarose gels, were scanned and quantitated using Image-Quant software (Molecular Dynamics).

Please replace paragraph [000168] with the following paragraph:

[000168] This randomized, double-blind, placebo-controlled study of bFGF in patients undergoing CABG demonstrates the safety and feasibility of this mode of therapy in patients with viable and ischemic but unrevascularizable myocardium. These results warrant a larger multicenter trial to assess the clinical benefit of this combination approach to myocardial revascularization, which is currently under way.

Please replace paragraph [000181] with the following paragraph:

[00181] Acute Hemodynamic Studies In five additional dogs of either sex (weight, 19 to 22 kg), we compared the effects of intracoronary bFGF on coronary hemodynamic parameters with those of temporary coronary occlusion and intracoronary NTG. The studies were performed with the use of a standard open-chest model in which the LAD was isolated and instrumented with a Doppler flow probe to measure blood flow (Crystal Biotech). A 2F catheter was advanced retrogradely via a small proximal branch of the LAD into the left main vessel for administration of drugs. Blood flow responses after 10- and 20-second periods of LAD occlusion and after incremental doses of intracoronary NTG (1, 10, and 100 µg) were recorded to confirm the presence of coronary vascular reactivity. Incremental doses of intracoronary bFGF (1, 10, and 100 µg) were then given, and coronary flow responses were measured. bFGF (buffered as described above) and NTG solutions were prepared in 1 mL of normal saline just before administration and were given as boluses over 20 seconds. Blood pressure, heart rate, and ECG were monitored continuously throughout the procedure. Coronary vascular resistance (CVR) was calculated according to the formula:

$$CVR \text{ (mmHg} \bullet \text{mL}^{-1}) = \text{mean aortic pressure (mm Hg)} \times 1/\text{coronary flow (mL/min)}$$

Please replace paragraph [000191] with the following paragraph:

[000191] Cardiac Deposition. Total specific activity (1 h) was $0.88 \pm 0.89\%$ for IC and $0.26 \pm 0.08\%$ for i.v. administration ($p = .12$) and decreased to $0.05 \pm 0.04\%$ ($p = .05$, compared with 1 h values) and $0.04 \pm 0.01\%$ ($p < .001$, compared with 1 h values) at 24 h, respectively. There were no differences between epicardial and endocardial deposition for both IC delivery; the results were pooled for further analysis. For IC delivery, LAD territory activity per gram of tissue (1 h) was $0.01 \pm 0.007\%$ and $0.008 \pm 0.008\%$ for normal and ischemic animals, and at 24 h dropped to $0.0005 \pm 0.0009\%$ (20-fold reduction) in nonischemic animals and $0.0008 \pm 0.0005\%$ (10-fold reduction) in ischemic animals. For i.v. delivery, 1-h LAD territory activity per gram of tissue was $0.003 \pm 0.001\%$ (3-fold reduction, $p = .2$, compared with IC) and $0.002 \pm 0.0009\%$ (4-fold reduction, $p = .3$, compared with IC) for normal and ischemic animals, and at 24 h dropped to $0.0004 \pm 0.0001\%$ (7.5-fold reduction) in nonischemic animals and $0.0004 \pm 0.0004\%$ (5-fold reduction) in ischemic animals, respectively. For 1-h LCX myocardial deposition, IC and i.v. deliveries resulted in a specific activity per gram of tissue of $0.008 \pm 0.004\%$ and $0.003 \pm 0.001\%$ (2.6-fold reduction, $p = .09$) in normal animals and $0.01 \pm 0.007\%$ and $0.003 \pm 0.001\%$ (3.3-fold reduction, $p = .2$) in ischemic animals, respectively. At 24 h, LCX deposition for IC and i.v. delivery dropped to $0.0006 \pm 0.0008\%$ and $0.0005 \pm 0.0002\%$ in normal animals and $0.0006 \pm 0.0006\%$ and $0.0004 \pm 0.0004\%$ in ischemic animals, respectively. For all groups, RCA myocardial distribution was similar to LAD and LCX distribution for i.v. administration. However, for IC delivery, RCA myocardial deposition was significantly lower than LAD or LCX myocardial deposition, because the radiolabel was infused in the left main coronary artery. Finally, for IC delivery, LCX/LAD territory activity was 79% and 154% for nonischemic and ischemic animals at 1 h and 116% and 75% for nonischemic and ischemic animals at 24 h, respectively. Intravenous administration resulted in an LCX/LAD activity of 97% and 100% for nonischemic and ischemic animals at 1 h and 123% and 98% for nonischemic and ischemic animals at 24 h, respectively.